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### Neurobiological and neuropsychological pathways into substance abuse and addictive behaviour

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# Neurobiological and neuropsychological pathways into substance abuse and addictive behaviour

## Abstract

"Addiction," derived from the Latin verb *addicere* (meaning "to enslave"), is characterized by the apparent "loss of control" or autonomy over one's behavior. Indeed, the continued use of substances by addicted individuals, despite an apparent awareness of the adverse negative consequences, suggests that addictive behavior may involve deficits in inhibitory control, decision-making and the regulation of affect (Bechara *et al.*, 2001; Fillmore, 2003; Goldstein & Volkow, 2002; Grant *et al.*, 2000; Jentsch & Taylor, 1999; Lubman *et al.*, 2004; Yücel & Lubman, 2007). Recent neuropsychological and neuroimaging studies across a variety of substance-using populations support this notion, implicating impairments in frontal cortical systems critically involved in executive control (Everitt *et al.*, 2001; Rogers & Robbins, 2001). However, an important question that remains is why only a minority of individuals who experiment with addictive substances develop problematic substance-use patterns. This chapter explores this issue from a neuropsychological perspective, specifically focusing on the neuropsychological aspects of addictive behavior (including neuroimaging findings where relevant) under three main sections:

- (1) *Neuropsychological sequelae of specific substances and their role in addictive behaviors*. This section will briefly discuss the evidence for specific neuropsychological and neurobiological effects of several major classes of substances including alcohol, cannabis, inhalants, stimulants, opiates and ecstasy. The section ends with a summary of the major findings across the various substances, highlighting consistent evidence for problems in prefrontally mediated functions (such as inhibitory control, decision-making and affect regulation).

## Keywords

Neurobiological, neuropsychological, pathways, into, substance, abuse, addictive, behaviour

## Disciplines

Arts and Humanities | Life Sciences | Medicine and Health Sciences | Social and Behavioral Sciences

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## Neurobiological and neuropsychological pathways into substance abuse and addictive behavior

Murat Yücel, Dan I. Lubman, Nadia Solowij and Warrick J. Brewer

### Introduction and overview

"Addiction," derived from the Latin verb *addicere* (meaning "to enslave"), is characterized by the apparent "loss of control" or autonomy over one's behavior. Indeed, the continued use of substances by addicted individuals, despite an apparent awareness of the adverse negative consequences, suggests that addictive behavior may involve deficits in inhibitory control, decision-making and the regulation of affect (Bechara *et al.*, 2001; Fillmore, 2003; Goldstein & Volkow, 2002; Grant *et al.*, 2000; Jentsch & Taylor, 1999; Lubman *et al.*, 2004; Yücel & Lubman, 2007). Recent neuropsychological and neuroimaging studies across a variety of substance-using populations support this notion, implicating impairments in frontal cortical systems critically involved in executive control (Everitt *et al.*, 2001; Rogers & Robbins, 2001). However, an important question that remains is why only a minority of individuals who experiment with addictive substances develop problematic substance-use patterns. This chapter explores this issue from a neuropsychological perspective, specifically focusing on the neuropsychological aspects of addictive behavior (including neuroimaging findings where relevant) under three main sections:

- (1) *Neuropsychological sequelae of specific substances and their role in addictive behaviors.* This section will briefly discuss the evidence for specific neuropsychological and neurobiological effects of several major classes of substances including alcohol, cannabis, inhalants, stimulants, opiates and ecstasy. The section ends with a summary of the major findings across the various substances, highlighting consistent evidence for problems in prefrontally mediated functions (such as inhibitory control, decision-making and affect regulation).

- (2) *Premorbid neuropsychological vulnerability to addictive behaviors.* Here we discuss how early difficulties in prefrontally mediated tasks of behavioral regulation can render the individual at risk for developing an addictive disorder. There is also a discussion of how problems in neurobehavioral disinhibition may manifest and be exacerbated by genetic polymorphisms, personality traits and comorbid disorders (medical, neurological or psychiatric), resulting in an increased vulnerability to addictive behavior.
- (3) *Adolescence: a key neurodevelopmental period of vulnerability.* This section focuses on the changes that occur in the adolescent brain. We discuss how premorbid vulnerabilities may impact upon this critical period of development.

Finally, we summarize how substance-associated neuropsychological impairments may interact with premorbid neuropsychological vulnerabilities and the adolescent period to render an individual at increased risk for addictive disorders.

### Neuropsychological sequelae of specific drugs and their role in addictive behavior

#### Alcohol

The most consistent findings of neuropsychological impairment in heavy and long-term drinkers of alcohol are in the domains of attention, short-term memory, visuospatial abilities, postural stability and executive functions (such as problem-solving, mental flexibility, judgment, working memory, response inhibition and

decision-making), with a relative sparing of declarative memory, language skills and primary motor and perceptual abilities (Bowden-Jones *et al.*, 2005; Corral-Varela & Cadaveira, 2002; Fishbein *et al.*, 2006; Goudriaan *et al.*, 2006; Scheurich, 2005). The link between lifetime exposure and the development of cognitive problems is unclear. While some research findings suggest that cognitive performance worsens in direct proportion to the frequency and duration of drinking (Beatty *et al.*, 2000; Parsons, 1998), other findings suggest that cognitive deficits may be detectable only in those who have been drinking regularly for at least 10 years (Eckardt *et al.*, 1998; Parsons & Nixon, 1998). These contrasting findings highlight the need for further research to determine how patterns of alcohol use are related to cognitive impairment, especially in light of some evidence to suggest that long-term, light-to-moderate social drinkers have also been found to have cognitive deficits (Parsons, 1998).

The nature of the neuropsychological deficits observed in long-term drinkers is consistent with disruption to the fronto-temporal, fronto-parietal and cerebellar brain systems. Indeed, structural MRI reveals a consistent association between heavy drinking and structural neuronal injury and volume loss that is more extensive in the frontal lobe, temporal lobe and cerebellum (Mann *et al.*, 2001; Pfefferbaum *et al.*, 1997). Results of autopsy studies show that individuals with a history of chronic alcohol consumption have smaller, lighter and more shrunken brains than non-alcoholic adults of the same age and gender (Hommer *et al.*, 1996, 2001). However, the evidence for this is not always consistent (Hommer, 2003; Wang *et al.*, 2003).

Some alcohol-related cognitive impairment and structural brain deficits can be reversed with abstinence over a period of several months to years (Corral-Varela & Cadaveira, 2002). Compared with treated alcoholics who subsequently relapsed to drinking, abstinence-associated improvements have been documented in neuropsychological functions such as working memory, visuospatial functioning and attention, and are accompanied by significant increases in brain volume (Sullivan *et al.*, 2000a, 2000b; Volkow *et al.*, 1994).

## Cannabis

Neuropsychological studies of chronic cannabis users in the unintoxicated state have demonstrated impaired performance on a variety of attention, memory and

executive function tasks (Bolla *et al.*, 2002; Fletcher *et al.*, 1996; Pope & Yurgelun-Todd, 1996; Pope *et al.*, 2001, 2003; Solowij *et al.*, 2002). Deficits have been attributed to duration of cannabis use (Solowij *et al.*, 2002), frequency of cannabis use (Pope *et al.*, 2001) or cumulative dosage effects (Bolla *et al.*, 2002). For example, impaired verbal learning and memory performance was found in heavy cannabis users but not light users, regardless of duration of cannabis use (Pope & Yurgelun-Todd, 1996; Pope *et al.*, 2001); comparable findings were also reported in long-term but not short-term cannabis users (e.g. 34 vs 8 years of use (Fletcher *et al.*, 1996); 24 vs 10 years of use (Solowij *et al.*, 2002)), even when both groups were using cannabis on a near daily basis (Solowij *et al.*, 2002). Performance on executive tests, such as the Stroop task (Eldreth *et al.*, 2004), is not consistently impaired in cannabis users, but performance decrements have nevertheless been shown to be related to duration of use (Solowij *et al.*, 2002), or dose interacting with lower IQ (Bolla *et al.*, 2002). Few studies have sought to specifically tease out differential impairments associated with varying patterns of cannabis use (e.g. heavy daily use for short periods vs light weekly use for long periods). Solowij *et al.* (1995) showed that the ability to focus attention and filter out irrelevant information was progressively impaired with increasing years of cannabis use, while speed of information processing was impaired with increasing frequency of use (days per month).

Recent neuroimaging studies of cannabis users demonstrate impaired performance in attention, verbal memory (Block *et al.*, 2000; Solowij *et al.*, 2004), working memory (Kanayama *et al.*, 2004), response inhibition (Eldreth *et al.*, 2004; Gruber & Yurgelun-Todd, 2005; Smith *et al.*, 2004) and decision-making tasks (Bolla *et al.*, 2005), with concomitant alterations in blood flow, activation or brain-tissue density primarily in prefrontal cortical, anterior cingulate, basal ganglia, cerebellar and hippocampal regions. For example, Matochik *et al.* (2005) found gray and white matter density changes in 28-day abstinent cannabis users in the medial temporal regions, and some of the density changes were associated with duration of cannabis use. Moreover, altered frontal cortical activation is apparent in cannabis users despite normal Stroop task performance (Eldreth *et al.*, 2004; Gruber & Yurgelun-Todd, 2005), suggesting that there may be disturbances in brain physiology that are not as yet apparent behaviorally.

The extent of persistence of effects or recovery of function following abstinence is also uncertain, with some studies suggesting no recovery after 25–28 days abstinence (Bolla *et al.*, 2002, 2005; Eldreth *et al.*, 2004), whilst others report full recovery after 28 days abstinence (Pope *et al.*, 2001) and partial early recovery after 2 years abstinence (Solowij *et al.*, 1995).

## Inhalants

While the toxic effects of chronic inhalant abuse are well described (Lubman *et al.*, 2006; Rosenberg *et al.*, 2002), there is only a small research literature examining the neurobiological and neuropsychological effects of voluntary exposure to this class of drugs (Brust, 1993; Fiedler *et al.*, 2003; Lubman *et al.*, 2006). One of the earliest neuropsychological investigations of inhalant abuse showed that inhalant abusers (mainly those abusing metallic paints) had deficits in motor coordination, learning, memory, executive functioning and overall verbal intelligence (Berry *et al.*, 1977; Maruff *et al.*, 1998). Cairney and colleagues have conducted a number of studies examining the effects of petrol sniffing on cognitive outcomes (Cairney *et al.*, 2002, 2004b, 2004a). They report that petrol sniffers (mean age 30 years) who have recovered from lead encephalopathy continue to demonstrate considerable neurological and cognitive impairments, including impaired visual attention, visual recognition memory and visual paired associate learning. Petrol sniffers who had not suffered lead encephalopathy demonstrated only mild deficits. One of the largest investigations examining the effects of inhalant use on neuropsychological functioning in adolescents was conducted by Chadwick *et al.* (1989). Those who had used volatile substances performed significantly worse on tests of vocabulary and impulsivity, and had significantly lower verbal and full-scale IQ. However, these differences were no longer significant when background social disadvantage was taken into account, although it is important to note that the inhalant group consisted of primarily experimental or recreational users.

From a neurobiological perspective, there is more conclusive evidence that inhalant exposure is associated with adverse consequences. A recent study comparing 55 inhalant abusers (mean age 30 years) and 61 cocaine abusers (mean age 29 years) found substantial brain abnormalities (especially in subcortical and white matter regions) and cognitive impairment within both

groups (Rosenberg *et al.*, 2002). However, the structural brain abnormalities were more common (44% vs 25%) and more extensive in the inhalant-using group. In addition, this group performed significantly worse on tests of working memory and tests requiring focused attention, planning and problem-solving. Interestingly, even within the inhalant-using group, solvent abusers had more extensive and severe abnormalities in brain white matter than other inhalant users, and these abnormalities were associated with greater cognitive impairment. For example, the 12% of solvent abusers who had diffuse moderate to severe white matter abnormalities had a mean verbal IQ score that was nearly 20% lower than the already low average score registered by the rest of the inhalant group. Thus, it appears that the nature and extent of neurobiological and neuropsychological impairment is associated with the length and chronicity of the abuse, as well as the type/composition of the volatile substance. Similar findings have been observed in other neurobiological and neuroimaging studies of chronic solvent exposure in occupational settings (Yamanouchi *et al.*, 1995, 1997).

Very few studies have specifically investigated recovery of function after prolonged exposure to inhalants. Cairney *et al.* (2004b, 2005) found significant improvements in previously identified neurobehavioral impairments following 2 years of abstinence. In fact, in many cases these deficits normalized completely. However, while those with the greatest levels of impairment showed the greatest degree of improvement with abstinence, they were less likely to recover completely.

## Opiates

Research on the long-term neuropsychological effects of chronic opiate abuse has been relatively limited. Davis and colleagues reported that 60% of individuals currently abusing opiates had impairments of at least two standard deviations below published norms on two or more neuropsychological tests, a significantly higher incidence than found in matched controls with no history of drug abuse (Davis *et al.*, 2002). In particular, deficits were identified in impulse control in those with a history of 5 or more years of heroin use. Similarly, Pau *et al.* (2002) examined the impact of heroin on frontal executive functioning in three cognitive domains, namely attention, impulse control and mental flexibility. They found that heroin abuse had adverse effects on impulse control but not attention or



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mental flexibility. Other studies have reported more diffuse deficits across the domains of attention, working memory, memory and executive function in chronic opiate abusers (Guerra *et al.*, 1987; Lee & Pau, 2002; Ornstein *et al.*, 2000; Pau *et al.*, 2002; Rogers *et al.*, 1999). Ornstein and colleagues found that heroin addicts were impaired on performance of cognitive tasks (e.g. learning, spatial working memory, strategic thinking) known to be sensitive to cortical damage (including selective lesions of the temporal and frontal lobes) (Ornstein *et al.*, 2000). Darke *et al.* (2000) reported that methadone-maintained heroin addicts performed more poorly on all neuropsychological domains tested, including attention (information processing speed, attentional capacity), memory (visual and verbal learning and memory) and executive functioning (problem-solving) compared with matched controls.

Chronic opiate- and amphetamine-using populations have been shown to have disturbances in prefrontal cortical activity, which was associated with performance on a task involving a decisional conflict between an unlikely high-reward option and a likely low-reward option (Ersche *et al.*, 2005). Moreover, this disturbance was observed in a group of drug users who had been abstinent for at least 1 year. Further support for prefrontal dysfunction comes from the large structural imaging study of Lyoo *et al.* (2006), which investigated gray matter density across the brain in 63 opiate-dependent subjects and 46 matched controls. These authors found that relative to controls, the opiate-dependent group exhibited significantly decreased gray-matter in the prefrontal, as well as superior temporal cortex, insula and fusiform gyrus. Another study by Kivisaari *et al.* (2004) in long-term opiate users found that the sylvian fissures and ventricles were wider in opiate-dependent subjects than in controls, which may be related to brain atrophy within frontal and temporal lobes.

Studies evaluating the persistence of cognitive deficits amongst abstinent opiate addicts remain mixed. A number of studies have found that abstinent groups of recovering addicts have no significant cognitive deficits (Davis *et al.*, 2002; Guerra *et al.*, 1987). Guerra *et al.* (1987) reported that individuals with current heroin abuse demonstrated deficits in attention, working memory, episodic memory and verbal fluency, which normalized 7–14 days following rapid detoxification. However, two other studies of abstinent heroin users (8 and 14 months, respectively)

reported ongoing deficits in executive function (Lee & Pau, 2002; Pau *et al.*, 2002). Using a more sophisticated battery of experimental neuropsychological tests, Ersche *et al.* (2006) reported that opiate-dependent individuals demonstrated marked impairments in spatial planning, paired associate learning and visual pattern recognition compared with matched controls. Performance of former opiate users (abstinent for 8 years on average) was not statistically different from current users on any measure, suggesting that the deficits observed did not simply reflect the current effects of drug use. These findings are in keeping with other studies describing prefrontal dysfunction in chronic drug users (Bechara *et al.*, 2001; Goldstein & Volkow, 2002; Jentsch & Taylor, 1999; Lubman *et al.*, 2004; Yücel & Lubman, 2007).

### Psychostimulants (cocaine, amphetamine/methamphetamine)

Few studies have explicitly attempted to examine cognitive functioning amongst methamphetamine users. Some researchers point to studies that suggest memory and executive problems, whilst others maintain that no firm evidence for a link exists (Maxwell, 2005). Recent studies of chronic amphetamine/methamphetamine abusers have shown that they perform poorly on decision-making tasks that involve regions of the frontal cortex (specifically the ventromedial prefrontal cortex), such that they make disadvantageous decisions that reflect valuing short-term gain over longer-term losses (Nordahl *et al.*, 2003; Rogers *et al.*, 1999). Methamphetamine users also appear to be more distractible and are unable to suppress processing task-irrelevant information (Nordahl *et al.*, 2003), which is consistent with their clinical presentation. Other work has also shown cognitive deficits related to processing speed, learning, delayed recall and inhibitory control and working memory (Gonzalez *et al.*, 2004; Rippeth *et al.*, 2004; Salo *et al.*, 2002). Another recent study found methamphetamine abuse to be associated with deficient strategic (i.e. executive) control of verbal encoding and retrieval, which is consistent with the proposed sequelae of methamphetamine-related prefronto-striatal circuit neurotoxicity (Woods *et al.*, 2005). Interestingly, comorbid cannabis use does not appear to exacerbate methamphetamine neurotoxicity, but rather has been suggested to have neuroprotective actions (Gonzalez *et al.*, 2004).

Neuropsychological studies of chronic cocaine users, like chronic amphetamine users, also demonstrate higher-order cognitive impairments (e.g. inhibitory dysregulation) that is consistent with abnormal blood flow in frontal brain regions (Strickland *et al.*, 1993). Several studies have reported that cocaine abuse is associated with decrements on neurobehavioral tests measuring executive control, visuo-perception, psychomotor speed, manual dexterity, verbal learning and memory (Bolla *et al.*, 1999; Rogers & Robbins, 2001). Ardila *et al.* (1991) found that neuropsychological test scores were correlated with lifetime amount of cocaine used, suggesting a direct relationship between cocaine abuse and cognitive impairment.

Neuroimaging studies of methamphetamine users have shown abnormalities of brain function relative to healthy controls including alterations of frontal, temporal and subcortical metabolism (Gouzoulis-Mayfrank *et al.*, 1999; Iyo *et al.*, 1997; Volkow *et al.*, 2001a, 2001b, 2001c). Changes in neuronal biochemistry that are suggestive of neuronal injury have also been found in the frontal cortex and basal ganglia (Ernst *et al.*, 2000). Using proton magnetic resonance spectroscopy (1H-MRS), Ernst *et al.* (2000) reported abnormally low levels of the neuronal marker N-acetylaspartate (NAA) in the basal ganglia of abstinent methamphetamine-dependent subjects. They also observed an inverse association between prefrontal white-matter NAA values and years of use, implying direct effects of this drug on neuronal integrity of the prefrontal tissue. Similar findings have been reported in the anterior cingulate cortex (Nordahl *et al.* 2002, 2005). Recent neuroimaging studies have shown that frontal and temporal lobe white matter continues to increase into the fifth decade of life (Bartzokis *et al.*, 2000). However, Bartzokis and colleagues found that cocaine-dependent subjects (aged 19 to 47) do not demonstrate the normal pattern of age-related increases in white matter within these brain regions (Bartzokis *et al.*, 2000), suggesting that continued cocaine use may arrest normal white matter maturation.

Examination of cognitive function in abstinent cocaine-dependent individuals after both 6 weeks and 6 months abstinence reveals persistent cognitive impairment across a wide range of functions compared with controls at both time points. Further, a close relationship between the degree of neuropsychological impairments and dosage (i.e. quantity

and dosage of peak usage) has also been reported (Di Sclafani *et al.*, 2002). Consistent with their neuropsychological findings, the authors also found that cocaine-induced brain volumetric reduction in the prefrontal cortex persists after 6 weeks of abstinence (Fein *et al.*, 2002).

### MDMA (N-methyl-3,4-methylenedioxy-amphetamine, ecstasy)

A number of persisting cognitive problems have been attributed to regular MDMA use and suggest underlying serotonergic dysfunction (Gouzoulis-Mayfrank & Daumann, 2006; McGuire, 2000; Montoya *et al.*, 2002). For example, impairments in memory (both visual and verbal) have been shown to correlate with in vivo measurements of brain serotonin function and levels of 5-HIAA in cerebrospinal fluid (CSF), as well as relating to the level of previous MDMA use (i.e. are dose related) (Bolla *et al.*, 1998). Other neuropsychological deficits that have been reported in regular ecstasy users include impairments of executive function and self-control (i.e. decreased inhibitory control and increased impulsivity) (McCardle *et al.*, 2004; Morgan *et al.*, 2005). McCardle *et al.* (2004) found that MDMA users exhibit difficulties in coding information into long-term memory, have impaired verbal learning, are more easily distracted and are less efficient at focusing attention on complex tasks. Interestingly, Spatt and colleagues have described a case of profound amnesia, associated with bilateral brain changes on MRI, following a single exposure to MDMA (Spatt *et al.*, 1997).

Although cognitive deficits among MDMA users have been well documented, little is known of the neurobiological sequelae of MDMA use. In one study, MDMA use in adolescence was associated with difficulties in the ability to focus and divide attention, as well as abnormal hippocampal activity during performance of a working-memory task (Jacobsen *et al.*, 2004). Other functional MRI studies have found abnormal fronto-temporal, parietal and subcortical activity during performance of working-memory tasks (Daumann *et al.*, 2001, 2003, 2004, 2005). Additionally, Daumann *et al.* (2003) found that relative to a group of controls and currently abstinent but previously moderate users, currently abstinent but previously heavy users showed more prominent frontal and temporal lobe activation abnormalities during performance of a working-memory task.

Structural MRI findings amongst MDMA polydrug users include evidence of diffuse gray matter reductions across the cortex, cerebellum and brainstem (Cowan *et al.*, 2003).

Little is known about the possible persistent neuropsychological effects of extensive MDMA use. However, there is tentative evidence that these cognitive deficits persist for at least 6 months after abstinence, whereas anxiety and hostility remit after a year of abstinence (Gouzoulis-Mayfrank & Daumann, 2006; Morgan *et al.*, 2002). Morgan *et al.* (2002) compared four groups of participants: current regular recreational MDMA users, ex-regular MDMA users who had abstained from using the drug for an average of 2 years, polydrug users who had never taken MDMA, and drug-naïve controls. They found that both current and ex-MDMA users exhibited elevated psychopathology and behavioral impulsivity compared with polydrug users and drug-naïve controls, but current MDMA users exhibited a broader range of psychopathology than ex-users. Both groups of MDMA users also exhibited impaired working memory and verbal recall performance compared with drug-naïve controls. These findings suggest that selective impairments of neuropsychological performance associated with regular MDMA use are not reversed by prolonged abstinence. This is consistent with evidence that MDMA may affect brain serotonergic systems in human users. Other studies have also found altered neural activations suggestive of prefrontal neuronal injury in abstinent MDMA users during performance of working-memory tasks (Daumann *et al.*, 2004).

## Summary of findings

In summary, the findings suggest that chronic substance abuse across a wide range of addictive substances can adversely affect neuropsychological functioning. While there is marked inter-individual variability in the patterns of substance use (e.g. duration, frequency, dosage), almost all substances have been found to affect the domains of attention, learning and memory, visuospatial abilities and executive functioning. Similarly, the neurobiological findings from structural, functional and spectroscopic MRI studies suggest dysfunction in neural systems that subserve these functions, particularly the fronto-temporal circuitry. The findings of impaired inhibitory control (variously referred to as response inhibition, inhibitory

regulation, self-control or impulsivity), working memory and decision-making, together with prefrontal imaging abnormalities, appear to be the most consistent findings across studies and substances.

It is important to note, however, that pathways into addiction are invariably complex, which makes it hard to disentangle the neuropsychological effects of substance abuse from associated risk factors. For example, while the study by Chadwick *et al.* (1989) identified a number of neuropsychological deficits amongst inhalant-using teenagers, these were not significantly different from non-users when background social disadvantage was controlled. Similarly Darke *et al.* (2000), in their study of methadone-maintained opiate users, noted that the methadone group had high rates of poly-substance use, overdose, head injury and comorbid psychopathology. The authors found that the neuropsychological deficits identified were more characteristic of those with associated comorbidities, further raising issues regarding the specificity of findings reported. We still have only a limited understanding of the role of these associated factors in the nature and extent of neuropsychological deficits observed.

Another related issue in the field is our limited understanding of the degree to which the observed neuropsychological deficits are pre-existing (i.e. present prior to any substance abuse) and indeed predispose to addictive behavior. While in some instances, these deficits have been found to be dose-dependent, implying that they are a direct consequence of drug exposure, the fact that most studies are cross-sectional in nature means that it is not possible to categorically determine whether the identified deficits are a consequence of the drugs specifically, relate to pre-existing vulnerabilities, or are a combination of both. More recent research is attempting to tease these issues apart. The next section will focus on how early behavioral dysregulation, psychopathology and genetic polymorphisms may each be associated with disturbances to normal neuropsychological functioning, leaving the individual at risk of developing an addictive disorder.

## Premorbid neuropsychological vulnerability to addictive behaviors

### Risk-taking behavior

Initiation of substance use typically occurs during adolescence, a critical period of neural, cognitive (as reviewed below), emotional and social development.



Notably, adolescence is a period during which there is increased affective reactivity together with significant but more protracted neural maturation (Giedd *et al.*, 1999; Gogtay *et al.*, 2004; Paus, 2005; Paus *et al.*, 1999; Steinberg, 2005). This occurs in areas associated with core executive and self-regulatory skills, including inhibitory control and affect-regulation (reviewed in more detail in the next section; see also chapter 8). The developmental delay between increases in emotional arousability during early adolescence, and the subsequent maturation of neurobiological systems subserving self-regulatory competence that continues into late adolescence or early adulthood, results in a developmentally normative "mismatch." Adolescents are therefore left with a limited capacity for regulating strong affective and behavioral impulses. This, in turn, increases the likelihood of adolescents engaging in more impulsive, emotive and risky decisions, which often involve experimentation and social use of drugs and alcohol, the incidence of which sharply increases during adolescence (Steinberg, 2004, 2005). However, some individuals appear to have a greater "mismatch" than others and this may provide important clues as to whether the individual is more vulnerable to behavioral dysregulation and addictive behaviors.

### Behavioral dysregulation

While a certain degree of behavioral dysregulation can be considered a normal part of adolescence, current research shows that some young individuals are significantly more impaired in this regard. These individuals have been shown to not only be more vulnerable to experiment with and use substances socially, but also to develop addictive behaviors. For example, Tarter and colleagues (Kirisci *et al.*, 2004; Tarter *et al.*, 2003) recently conducted a cross-sectional and longitudinal analysis of children at low-risk and high-risk of substance use (on the basis of parental substance-use history) and found that deficits in behavioral regulation (referred to as "neurobehavioral inhibition") at age 16 in the high-risk children predicted a substance-use disorder (SUD) at age 19 with 85% accuracy. Their measure of behavioral regulation was derived using primarily prefrontal tests of cognition (e.g. Stroop interference task, Porteus mazes, motor restraint), affect (a temperament survey) and behavior (number of behavioral disorder symptoms). The indices derived from these

areas converge with other evidence to suggest that behavioral dysregulation is a key component of liability to addictive behavior.

### Behavioral and mental health disorders

Childhood and adolescence is also a time during which the incidence of behavioral and mental health disorders rises sharply (Lewinsohn *et al.*, 1993). Young people who have behavioral problems early (e.g. a difficult temperament in infancy, or childhood oppositional, aggressive or impulsive behaviors) are at increased risk of developing SUDs, especially males (Lewinsohn *et al.*, 1993). Childhood diagnoses of oppositional defiant disorder, conduct disorder and attention-deficit hyperactivity disorder are also well-established risk factors for youth SUD (Button *et al.*, 2006; Conway *et al.*, 2006; Hasin *et al.*, 2005; Kantojarvi *et al.*, 2006). In addition, a number of mental health disorders are also associated with the development of problematic substance use. Disorders such as depression, anxiety, schizophrenia, bipolar disorder and obsessive-compulsive disorder have high rates of comorbid substance use (Bogenschütz & Nurnberg, 2000; Brady & Sinha, 2005; Hides *et al.*, 2004; Swartz *et al.*, 2006). Given that deficits in inhibitory control and affect regulation are often found across many of these disorders, together with disruption to brain regions subserving these functions (e.g. prefrontal and temporal areas), it is possible that they form a key component of liability to not only behavioral and mental health disorders, but also to addictive behavior.

### Personality disorders

Certain personality characteristics may also influence an individual's decision to use drugs, as well as their liability to addictive behavior. Indeed, previously identified inhibitory-control and affect-regulation difficulties may be components of a premorbid personality style rather than the result of state-related cognitive-affective processes. To this end, there is a growing literature on temperament and personality as risk factors for SUDs and addiction. These studies highlight a relationship between measures of impulsivity and related constructs (such as risk-taking, sensation-seeking) in childhood and the development of later SUDs in adulthood (Tarter *et al.*, 2003). In fact, studies of both adolescents and adults consistently report an association between impulsivity (e.g. acting in a sudden and unplanned manner, acting

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without having all the necessary information or failing to think through the pros and cons of a decision) and substance-related problems (Acton, 2003; Dawe *et al.*, 2004; Stepp *et al.*, 2005). More recently, researchers have suggested that it is a specific domain of impulsivity, termed "rash-spontaneous impulsivity" (the tendency to act rashly and without consideration of consequences; see Dawe *et al.*, 2004) that is more directly associated with SUD.

Other personality traits such as negative affectivity/neuroticism have also been identified as risk factors for SUD. Negative affect/neuroticism is characterized by a general tendency to experience life as more negative, difficulty in controlling one's mood (i.e. difficulties with affect regulation), and/or being less tolerant to stressful life events. There is growing evidence to suggest that adolescent SUD may not only result in disinhibited behavior or impulsivity (reviewed above), but may in fact reflect an attempt to reduce negative affectivity (Chassin *et al.*, 1993, 2004). From a neurobiological and neuropsychological perspective, this inability to internally regulate moods and the over-reliance upon external agents, such as psychoactive substances, suggests inappropriate neural (particularly prefrontal) and cognitive modulation of emotions (Whittle *et al.*, 2006).

## Genetic polymorphisms

Genetic factors appear to account for 30–60% of the overall variance in risk for developing a drug addiction (Kreek *et al.*, 2005). While the precise mechanisms underlying this relationship remain unclear, recent work implicates the role of specific genetic polymorphisms. For example, studies investigating the catechol-*O*-methyltransferase (COMT) gene, which affects how long dopamine acts in the synapses of the prefrontal cortex, suggests that specific polymorphisms are less common in addicted populations. The methionine polymorphism, which results in a slower breakdown of prefrontal dopamine, is associated with better prefrontal cortical function (including working memory and inhibitory control) in both children (Diamond *et al.*, 2004) and adults (Egan *et al.*, 2001; Malhotra *et al.*, 2002). Interestingly, the polymorphism is significantly less common in drug-addicted populations, suggesting that this particular genetic vulnerability may be mediated by its effects on prefrontally mediated cognitive functioning (Beuten *et al.*, 2006; Li *et al.*, 2004).

## Summary of findings

Adolescence is a critical period of development, characterized by gradually maturing self-regulatory skills. The immaturity of these cognitive skills, compounded by increased emotional arousability at this time, may at least in part explain why adolescence represents such a period of vulnerability for risk-taking behavior, including experimentation and social use of drugs and alcohol. These developmental processes may be exaggerated in some individuals and partly underlie increased risk for behavioral and mental health disorders that also emerge during this period, together with associated neuropsychological impairments. In turn, behavioral and mental health problems, together with certain personality traits have been identified as major risk factors for SUDs. Given that deficits in inhibitory control and affect regulation are often found across many of these disorders, together with disruption to brain regions subserving such functions (e.g. prefrontal and temporal areas), it is possible that they represent a common component of a liability to SUDs and addictive behaviors more generally. Genetic factors that affect prefrontal cortical functioning may also further increase behavioral dysregulation and vulnerability to addiction.

## Adolescence: a key neurodevelopmental period of vulnerability

### Remodeling the prefrontal cortex and maturing executive abilities

As noted above, one critical characteristic of human brain development is an initial overproduction of gray matter, followed by a period of *pruning* during adolescence (Giedd *et al.*, 1999; Gogtay *et al.*, 2004; Paus, 2005; Paus *et al.*, 1999). This latter process results in a marked decline in synaptic connections, such that only synapses integral for optimal functioning are retained. Pruning is accompanied by *myelination*, a process that also makes the brain's operations more efficient, sometimes by 100-fold. Myelination does not occur concurrently in all brain regions – there is a graded progression of maturation with posterior and deep brain structures (regions responsible for more primitive functions) maturing earlier, while the medial and lateral frontal areas (regions responsible for higher-cognitive functions) continue

to develop well into adolescence and young adulthood. As such, while overall brain weight is not changing markedly as a result of the pruning of gray matter and the development of white matter, the composition of the brain is changing considerably during adolescence – often referred to as a ‘remodeling’ of the brain. Importantly, this remodeling associated with developmental maturation within frontal, temporal and parietal structures, mirrors the development of more complex cognitive (e.g. inhibitory/impulse control, working memory, decision-making and other cognitive processes that encompass the executive suite), as well as affective abilities (e.g. capacity to regulate motivational drive, affect and social cognition) (Giedd *et al.*, 1999; Gogtay *et al.*, 2004; Paus, 2005; Paus *et al.*, 1999). Given that the prefrontal cortex undergoes dramatic developmental changes from adolescence to adulthood, drug administration during adolescence may have greater impact on behaviors, which are mediated by this region. Indeed, there is limited but growing evidence that adolescents appear to be more vulnerable than adults to the adverse neuropsychological and neurobiological effects of substance use (Scheier & Botvin, 1995). Some evidence for this comes from studies of teenage alcohol and cannabis use.

### Alcohol and its effects on adolescent brain development

Adolescents who misuse alcohol show greater neuropsychological deficits on learning, memory and executive brain function than adults who misuse alcohol, a finding that might stem from the adverse effects of alcohol on the development and maturation of brain regions such as the hippocampus and prefrontal cortices. For example, De Bellis and colleagues compared the hippocampal volumes of adolescents and young adults with alcohol-use disorders (aged 13–21 years) to those of healthy matched controls (De Bellis *et al.*, 2000). They found that the size of the hippocampus was significantly smaller in subjects with alcohol problems, and that its volume positively correlated with age of first use and negatively correlated with duration of use. More recently, they reported that adolescents with alcohol-use disorders had smaller prefrontal cortices and white matter volumes compared with matched controls (De Bellis *et al.*, 2005). Further, prefrontal cortical volumes significantly correlated with measures of alcohol consumption. While interpretation of these studies is limited

by their cross-sectional nature and the high rates of other types of psychopathology among the participants with alcohol-use disorders, they suggest that adolescents may be particularly vulnerable to the effects of alcohol on learning, memory and executive brain function.

### Cannabis and its effects on adolescent brain development

With respect to cannabis, early-onset cannabis users have also been found to have smaller whole brain volume, lower percent cortical gray matter, higher percent white matter, and increased resting cerebral blood flow compared with late-onset users (Wilson *et al.*, 2000). There is growing evidence that individuals who initiate cannabis use at an early age, when the brain is still developing, might be more vulnerable to lasting neuropsychological deficits than individuals who begin using later in life. Early-onset cannabis use (prior to age 16 or 17), but not late-onset cannabis use (after age 17), was shown to impair attentional processes measured by reaction time during visual scanning (Ehrenreich *et al.*, 1999), visual search and short-term memory (Huestegge *et al.*, 2002), and resulted in greater reduction of P300 amplitudes in an attention task (Kempel *et al.*, 2003). Cannabis users who had commenced use prior to age 17 were more impaired than late-onset cannabis users on measures of learning and executive functions (Pope *et al.*, 2003) and were the least likely to show recovery of cognitive functions after 28 days abstinence (Harrison *et al.*, 2002). Jacobsen *et al.* (2004) found that adolescent cannabis users showed impaired performance on executive tasks such as the Continuous Performance Task and in an n-back working-memory task, which was accompanied by failure to deactivate the right hippocampus (measured by fMRI).

### Summary of findings

There is emerging evidence that early-onset alcohol and cannabis use is associated with a range of later negative outcomes. However, it is not clear whether those who initiated substance use early have pre-existing neuropsychological deficits or whether any reported deficits are a direct consequence of early-onset substance use. Recent animal work supports the latter notion, with studies finding that adolescence may be associated with an increased sensitivity to the

neurotoxic properties of addictive drugs. However, it is likely that any additional pre-existing compromise to the behavioral-regulatory system (e.g. through associated psychopathology or genetic polymorphisms) may further widen the "mismatch" between developmental trajectories, leading to greater behavioral dysregulation and vulnerability to addictive behaviors.

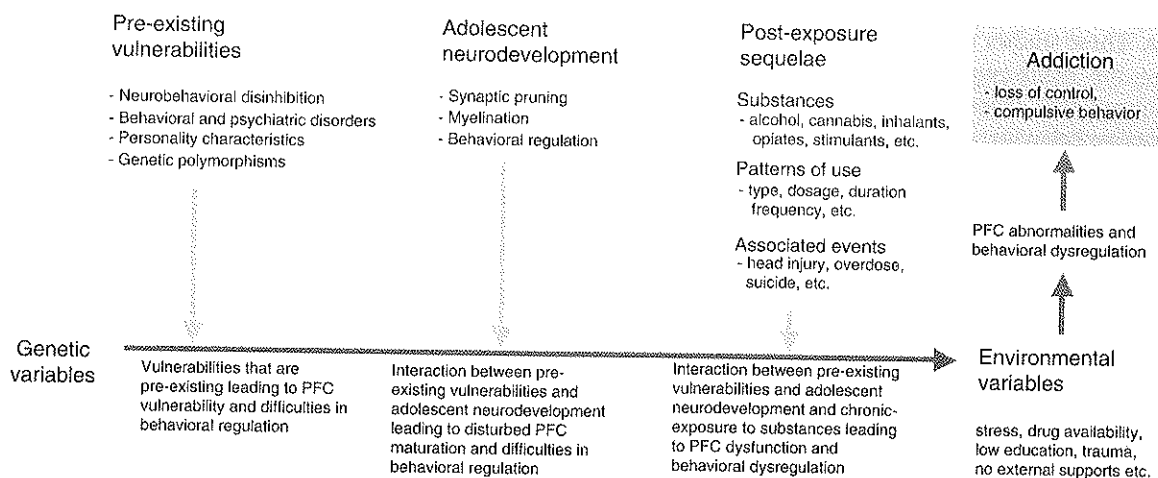
## Summary and conclusions

There is now a large body of evidence suggesting that addicted individuals have neuropsychological impairments in the domains of attention, learning/memory and executive functioning, as well as associated neurobiological abnormalities involving fronto-temporal and basal ganglia circuits. In some instances, these deficits have been found to be dose-dependent, implying that they are a direct consequence of prolonged drug exposure. However, the nature and extent of these deficits and the factors mediating them (e.g. patterns of drug use, polysubstance abuse, comorbidities) are still not fully clear. The fact that most studies are cross-sectional in nature means that it is not possible to categorically determine whether the identified deficits are a consequence of the drugs specifically, whether they relate to pre-existing vulnerabilities, or are a combination of both.

While more recent research is attempting to elucidate these issues of cause and effect, there is consistent evidence from research conducted in other disciplines to suggest that behavioral, personality and mental

health problems often manifest prior to SUD onset, suggesting that they are either specific risk factors for the development of SUDs, or share common risk factors. Indeed, inhibitory-control deficits are not only central to drug dependence/addiction but also to many behavioral, personality and mental health problems. This notion is also consistent with epidemiological data demonstrating that many of these conditions frequently co-occur, as well as neurobiological data showing overlapping abnormalities of the prefrontal, anterior cingulate, orbitofrontal and hippocampal regions – regions critically involved in inhibitory-control of behavior. In addition, recent genetic studies suggest a link between genetic predisposition and impaired cognitive functioning, with the notion that certain polymorphisms are significantly more common in drug-addicted populations.

Finally, brain regions subserving inhibitory control of behavior do not fully mature until midway through the third decade of life. Emerging evidence from alcohol and cannabis using populations suggests that early-onset substance use is associated with increased risk for a range of adverse outcomes. While the mechanisms that underlie this relationship are not fully understood, recent advances in developmental neuroscience, together with emerging literature on early-onset substance use, suggest that the adolescent brain may be more vulnerable to the effects of psychoactive drugs because of the unique and critical neurodevelopmental processes that are occurring during this period (e.g. maturation of inhibitory control and associated brain regions/connections).



**Figure 22.1.** Illustrations of how substance-associated neuropsychological sequelae may interact with adolescent neurodevelopment and pre-existing vulnerabilities rendering the individual at increasing risk for addictive disorders. PFC = prefrontal cortex.



So why do only a minority of individuals who experiment with alcohol and drugs develop problematic substance-use patterns? As illustrated in Figure 22.1, the pathways leading to drug addiction are likely to be both multi-faceted and complex. It seems probable that there is an intricate relationship between pre-existing neuropsychological vulnerabilities (described above), the age of initiation of substance use (or neurodevelopmental maturity), patterns of substance use (type, dosage, duration, frequency) and associated events (head injury, overdose, suicide). Clearly, each of these areas can impact upon the development and functional integrity of the prefrontal cortex (PFC), which is postulated to play an important role in the initiation and maintenance of drug-use behavior. Such adverse effects are likely to render the individual at increased risk for making decisions that are impulsive, focused on short-term gains, and lack inhibitory control. It is therefore not surprising that affected individuals find it difficult to regulate their drug-seeking and drug-taking behavior and frequently relapse. However, the nature and extent of the impact on PFC integrity is likely to depend on a number of factors from genetic through to environmental variables. Such relationships need further investigation, especially as neuropsychological studies comprehensively exploring these notions in a prospective and longitudinal manner have been limited to date. Nevertheless, this is an exciting time in drug-addiction research. There are currently several prospective, multi-method, multi-modal studies being conducted internationally that capture the relevant variables identified to date. These studies will soon provide further insights into the neuropsychological and neurobiological pathways that increase risk for the development of addictive behavior.

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